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(11) **EP 0 536 235 B1**

(12) **EUROPEAN PATENT SPECIFICATION**

(45) Date of publication and mention  
of the grant of the patent:  
**22.01.1997 Bulletin 1997/04**

(21) Application number: **91912173.1**

(22) Date of filing: **25.06.1991**

(51) Int. Cl.<sup>6</sup>: **A61K 9/12, A61K 9/72**

(86) International application number:  
**PCT/GB91/01023**

(87) International publication number:  
**WO 92/00061 (09.01.1992 Gazette 1992/02)**

(54) **PRESSURISED AEROSOL COMPOSITIONS**  
**DRUCKAEROSOLZUSAMMENSETZUNG**  
**COMPOSITIONS D'AEROSOL PRESSURISEES**

(84) Designated Contracting States:  
**AT BE CH DE DK ES FR GB GR IT LI LU NL SE**

(30) Priority: **29.06.1990 GB 9014526**  
**29.06.1990 GB 9014527**  
**03.11.1990 GB 9023953**

(43) Date of publication of application:  
**14.04.1993 Bulletin 1993/15**

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(56) References cited:  
**EP-A- 0 372 777** **WO-A-88/07855**  
**WO-A-90/11754** **GB-A- 2 046 093**

Remarks:

The file contains technical information submitted  
after the application was filed and not included in  
this specification

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## Description

This invention relates to pressurized aerosol compositions, in particular compositions of powdered inhalation medicaments.

Pressurized aerosols for the administration of medicaments, and indeed for other applications, conventionally contain one or more liquified chlorofluorocarbons (CFC's) as propellant. Such materials are suitable for use in such applications since they have the right vapour pressures (or can be mixed in the right proportions to achieve a vapour pressure in the right range) and are essentially taste- and odour-free.

In recent years there has been increasing concern about the depletion of the ozone layer in the upper atmosphere. This is believed to be due to the release into the atmosphere of CFC's and has led to a search for alternative agents for use in all applications of CFC's. To this end, aerosols for many applications are now pressurized using pressurized gases such as nitrogen or hydrocarbons. However, such propellants are generally not suitable for use in the administration of inhalation medicaments since they are toxic and/or the pressure within the canister falls each time the device is used which leads to unreproducible dosing.

The use of hydrofluorocarbons as aerosol propellants has also been suggested but this has the disadvantage that other excipients, in particular the surfactants generally used in aerosol formulations, such as sorbitan trioleate and oleic acid, are insufficiently soluble in these materials. Surfactants are required *inter alia* to ensure good dispersion of the powdered medicament and smooth operation of the valve through which the composition is dispensed.

European Patent Application 0 372 777 offers a solution to the problem of poor solvating properties of the hydrofluorocarbons by adding to the formulation a solvent, eg ethanol, capable of increasing the solubility of the surfactant in the propellant. This apparent solution suffers from the disadvantage that many of the solvents ("adjuvants") suggested are flammable, toxic and/or affect the stability and dispersion characteristics of the formulation.

Surprisingly, we have found a group of surfactants having a particular structural feature which are sufficiently soluble in hydrofluorocarbon propellants to permit the formulation of satisfactory pressurized aerosol formulations without the need for additional solvents.

Thus, according to the invention there is provided a pressurized aerosol composition comprising a medicament, a hydrofluorocarbon propellant and a polyethoxylated surfactant, the composition containing no solvent, other than the propellant, capable of increasing the solubility of the surfactant in the propellant.

The compositions according to the invention are advantageous in that the solubility of the surfactant is such as to ensure good dispersion of the medicament and smooth operation of the aerosol valve. In addition, certain of the formulations disclosed herein are advantageous over prior art formulations in that they are more stable, are less toxic, have more suitable vapour pressures for the administration of medicaments by inhalation, more readily produced, perform better, eg in dispersion tests carried out using an impinger, or have other advantageous pharmaceutical properties.

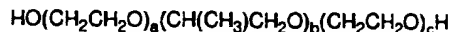
The propellant mixtures of the present invention may also be advantageous in that they are substantially taste- and odour-free and have suitable vapour pressures for the administration of medicaments by inhalation, yet are environmentally safe and acceptable, especially when compared with compositions including chlorofluorocarbons. In addition, they may be less irritant than corresponding compositions including conventional surfactants such as oleic acid and sorbitan trioleate.

We prefer surfactants which have an average number, *n*, of from 2 - 50, more preferably 2 - 40, particularly 2 - 30, and especially 4 - 20, polyethoxylate units per molecule of surfactant.

Although the surfactant may consist completely of polyethoxylate units, ie is polyethylene glycol, eg having an average molecular weight of from 200 to 4000, we prefer surfactants in which the polyethoxylated portion is from 10 - 90%, more preferably 10 - 70%, particularly 10 - 50% by weight of the surfactant.

We prefer surfactants having an average molecular weight of less than 20,000, more preferably less than 10,000 and particularly less than 5000. We prefer surfactants having an average molecular weight greater than 200, more preferably 400 and especially 1000.

We prefer surfactants which are block copolymers of ethylene oxide and propylene oxide, particularly those polymers known as poloxamers. These surfactants have the general formula



in which *a* and *c* are generally in the range 2 to 130 and *b* is in the range 15 to 67; these compounds are block copolymers with the polyethoxylate portions accounting for between 20 and 90% by weight. These surfactants are available under the registered trademark Synperonic PE (ICI) and the registered trademark Pluronic (BASF). Particularly suitable poloxamers include the following Synperonic PE surfactants:

L35, L42, L44, L61, L62, L62F, L64, L75, L81, P85, L92 P94, L101 and L121;

in which L indicates that the surfactants are liquids, P that they are pastes, the first digit is a measure of the molecular weight of the polypropylene portion of the surfactant and the last digit of the number, multiplied by 10, gives the per cent ethylene oxide content of the surfactant. Further characterizing details of these surfactants, and the major-

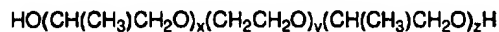
ity of surfactants described herein, are given in Surfactants Europa, 2nd Edition, 1989, compiled and edited by Gordon L. Hollis and published by Tergo-Data, the entire contents of which are hereby incorporated by reference.

Other suitable poloxamers include the following Pluronic PE surfactants:

3100, 4300, 6100, 6200, 6400, 8100 and 9200.

We prefer poloxamers which contain less than 60% by weight of ethylene oxide.

We also prefer block copolymers of ethylene oxide in which a polyethylene glycol moiety has been used as the initiator molecule for the polymerisation, giving compounds of the general formula:



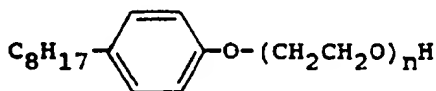
which typically have a molecular weight of the order of 3000 with the ethylene oxide portions accounting for typically 10-20% by weight; these compounds are available under the tradename Synperonic RPE (ICI) and Pluronic RPE (BASF).

Especially preferred surfactants include Pluronic RPE2510, RPE2520 and RPE3110.

We prefer surfactants having a hydrophobic portion derived from an alkylphenol, an alcohol or ethylenediamine.

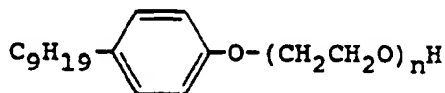
Particular surfactants derived from an alkylphenol that may be mentioned include

a) compounds of the general formula



in which n represents the average number of ethoxylate groups per molecule; these compounds are available under the registered trademark Synperonic OP (ICI), and

b) compounds of the general formula



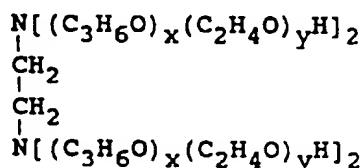
in which n represents the mean number of ethoxylate groups per molecule; these compounds are available under the tradename Synperonic NP (ICI). Suitable examples of these surfactants include the following Synperonic surfactants:

NP4, NP5, NP6, NP7, NP8, NP9, NP10, NP12, NP15, OP10 and OP11.

Alcohol derived surfactants may be derived from a mono-hydric or polyhydric alcohol. Particular mono-hydric alcohols that may be mentioned include straight or branched chain  $\text{C}_8$  to  $\text{C}_{20}$  alcohols. Suitable surfactants that may be mentioned include the alcohol ethoxylates available under the tradename Synperonic LF (ICI).

Polyhydric alcohols from which the surfactant may be derived include glycerol and sorbitan. The polyhydric alcohol may be partially esterified, eg, with a fatty carboxylic acid, such as lauric, palmitic and especially oleic acid. We particularly prefer surfactants which are polyethoxylated derivatives of sorbitan mono-oleate, for example, polysorbate 20, 40, 60 and 80.

Surfactants having a portion derived from ethylenediamine that may be particularly mentioned include the Synperonic T series of compounds (ICI) of general formula



in which x and y are in the ranges 4-25 and 1-120 respectively. Particular examples of these surfactants that may be

specifically mentioned include Synperonic T701, T304 and T702

In the present context, the term 'hydrofluorocarbon' is to be taken to mean a compound of general formula



in which x is an integer from 1 to 3,  $y+z=2x+2$  and y and z are both at least 1.

Particular hydrofluorocarbons of interest are  $CF_3CFH_2$  (Propellant 134a),  $CH_3CHF_2$  (Propellant 152a) and  $CF_3CHFCF_3$  (Propellant 227). We particularly prefer formulations containing Propellant 227.

In general the vapour pressure of the mixture should be in the range suitable and permitted for aerosol propellants.

The vapour pressure may be varied by mixing one or more hydrofluorocarbons and/or some other suitable vapour pressure modifying agent in appropriate proportions.

We prefer the vapour pressure of the mixture to be in the range 20 to 100 psi, more preferably 40 to 80 psi, eg about 60 psi.

The amount of surfactant in the composition will generally be from about 0.01 to 10% by weight, more preferably from about 0.1 to 5%, eg about 1%.

The properties of the invention, notably the absence of any co-solvent for the surfactant, render it particularly useful in the pharmaceutical field.

The medicament may be in solid, particulate form (ie the composition may be a suspension), or the active ingredient may be dissolved in the propellant.

Medicaments which may be dispersed in the composition according to the invention include any medicaments which are conventionally administered by inhalation of a pressurised aerosol formulation. Such medicaments include drugs for use in the prophylactic or remedial treatment of reversible obstructive airways disease, eg drugs such as sodium cromoglycate, nedocromil sodium, inhaled steroids such as beclomethasone dipropionate, tiotropium, fluticasone, anticholinergic agents such as ipratropium bromide, and bronchodilators, eg salmeterol, salbutamol, reproterol, terbutaline, fenoterol and salts thereof. We find that the formulations are particularly advantageous for formulating salts of carboxylic acids, particularly dicarboxylic acids such as nedocromil and cromoglycic acid.

Where the medicament is solid, it preferably has a particle size distribution such that a high proportion of the particles are of a size capable of penetrating deep into the lung. In particular, the active ingredient is preferably in a form having a mass median diameter of from 0.1 to 10  $\mu m$ , more preferably from 0.1 to 4  $\mu m$ , eg about 2 or 3  $\mu m$ .

We prefer the active ingredient to have a mass median diameter in the range 0.01 to 10 microns, more preferably from 1 to 5 microns. The composition preferably comprises from 0.05 to 15, preferably from 0.1 to 10, and most preferably from 0.5 to 5% w/w of the active ingredient.

In producing the compositions according to the invention, a container equipped with a valve is filled with a propellant containing the finely-divided medicament. The container may first be charged with a weighed amount of medicament which has been ground to a predetermined particle size, or with a slurry of powder in the cooled liquid propellant. The container may alternatively be filled by introducing powder and propellant by the normal cold filling method, or a slurry of the powder in one component of the propellant may be placed in the container, the valve sealed in place, and the balance of the propellant then introduced by pressure filling through the valve nozzle. As a further alternative a bulk quantity of the total composition may be filled into the container through the valve.

The invention is illustrated by the following example:

#### Example

Compositions were prepared by cold filling of the ingredients into aluminium aerosol canisters which were then sealed by crimping a 50  $\mu l$  or 100  $\mu l$  aerosol valve in place.

The following combinations of micronised active ingredient, surfactant and propellant were used:

5	1.	Nedocromil sodium	0.2000 g
		Synperonic PEL 62	0.0612 g
		HFC 134a	11.9788 g
10	2.	Nedocromil sodium	0.2000 g
		Pluronic PE 6200	0.0612 g
		HFC 134a	11.9788 g
15	3.	Nedocromil sodium	0.2000 g
		Synperonic NP 15	0.0612 g
		HFC 134a	11.9788 g
20	4.	Nedocromil sodium	0.2000 g
		Synperonic PEL 62	0.0706 g
25		HFC 227	13.8494 g
30	5.	Nedocromil sodium	0.2000 g
		Pluronic PE 6200	0.0706 g
		HFC 227	13.8494 g
35	6.	Nedocromil sodium	0.2000 g
		Synperonic NP15	0.0706 g
		HFC 227	13.8494 g
40	7.	Sodium cromoglycate	0.5000 g

	Synperonic PEL 62	0.0612 g
	HFC 134a	11.6788 g
5		
	8. Sodium cromoglycate	0.5000 g
	Pluronic PE 6200	0.0612 g
10	HFC 134a	11.6788 g
	9. Sodium cromoglycate	0.5000 g
	Synperonic NP 15	0.0612 g
15	HFC 134a	11.6788 g
	10. Sodium cromoglycate	0.5000 g
	Synperonic PEL 62	0.0706 g
20	HFC 227	13.5494 g
	11. Sodium cromoglycate	0.5000 g
25	Pluronic PE 6200	0.0706 g
	HFC 227	13.5494 g
	12. Sodium cromoglycate	0.5000 g
30	Synperonic NP 15	0.0706 g
	HFC 227	13.5494 g
	13. Nedocromil sodium	0.2000 g
35	Polyethylene glycol PEG 200	0.0706 g
	HFC 227	13.8494 g
40		
	14. Nedocromil sodium	0.2000 g
	Polyethylene glycol PEG 600	0.0706 g
45	HFC 227	13.8494 g
	15. Nedocromil sodium	0.2000 g
	Polysorbate 80	0.0706 g
50	HFC 227	13.8494 g
55		

16.	Nedocromil sodium	0.2000 g
	Polysorbate 20	0.0706 g
	HFC 227	13.8494 g
17.	Nedocromil sodium	0.2000 g
	Polysorbate 80	0.0122 g
	HFC 134a	12.0278 g
18.	Nedocromil sodium	0.2000 g
	Synperonic PEP 85	0.0122 g
	HFC 134a	12.0278 g

In all cases stable suspensions of the active ingredient in the propellant were obtained.

#### Claims

Claims for the following Contracting States : AT, BE, CH, LI, DE, DK, FR, GB, IT, LU, NL, SE

1. A pressurised aerosol composition comprising a medicament, a hydrofluorocarbon propellant and a polyethoxylated surfactant, characterised in that the composition contains no solvent, other than the propellant, capable of increasing the solubility of the surfactant in the propellant.
2. A composition according to Claim 1, wherein the surfactant has an average number of from 2 - 50 polyethoxylate units per molecule of surfactant.
3. A composition according to Claim 1 or 2, wherein the surfactant is a block copolymer of ethylene oxide and propylene oxide.
4. A composition according to Claim 1 or 2, wherein the surfactant has a hydrophobic portion derived from an alkylphenol, an alcohol or ethylenediamine.
5. A composition according to Claim 4, wherein the alcohol is a monohydric alcohol.
6. A composition according to Claim 4, wherein the alcohol is polyhydric.
7. A composition according to Claim 6, wherein the polyhydric alcohol is partially esterified.
8. A composition according to any one of Claims 1, 2, 4, 6 or 7, wherein the surfactant is polysorbate 20, polysorbate 40, polysorbate 60 or polysorbate 80.
9. A composition according to any one of the preceding Claims, wherein the propellant is selected from propellant 134a, propellant 152a and propellant 227.
10. A composition according to any one of the preceding Claims, wherein the propellant is propellant 227.

Claims for the following Contracting States : ES, GR

1. A process for the preparation of a pressurised aerosol composition comprising a medicament, a hydrofluorocarbon propellant and a polyethoxylated surfactant, and characterized in that it contains no solvent, other than the propellant, capable of increasing the solubility of the surfactant in the propellant, which process comprises mixing the

medicament and the surfactant with the propellant.

2. A process according to Claim 1, wherein the surfactant has an average number of from 2 - 50 polyethoxylate units per molecule of surfactant.
3. A process according to Claim 1 or 2, wherein the surfactant is a block copolymer of ethylene oxide and propylene oxide.
4. A process according to Claim 1 or 2, wherein the surfactant has a hydrophobic portion derived from an alkylphenol, an alcohol or ethylenediamine.
5. A process according to Claim 4, wherein the alcohol is a monohydric alcohol.
6. A process according to Claim 4, wherein the alcohol is polyhydric.
7. A process according to Claim 6, wherein the polyhydric alcohol is partially esterified.
8. A process according to any one of Claims 1, 2, 4, 6 or 7, wherein the surfactant is polysorbate 20, polysorbate 40, polysorbate 60 or polysorbate 80.
9. A process according to any one of the preceding Claims, wherein the propellant is selected from propellant 134a, propellant 152a and propellant 227.
10. A process according to any one of the preceding Claims, wherein the propellant is propellant 227.

#### Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, LI, DE, DK, FR, GB, IT, LU, NL, SE

1. Druckaerosolzusammensetzung, die ein Arzneimittel umfasst, ein Fluorkohlenwasserstofftreibgas, und einen polyethoxylierten oberflächenaktiven Stoff, dadurch gekennzeichnet, daß die Zusammensetzung kein Lösungsmittel außer dem Treibgas enthält, das die Löslichkeit des oberflächenaktiven Stoffs in dem Treibgas erhöhen kann.
2. Zusammensetzung nach Anspruch 1, in der der oberflächenaktive Stoff eine durchschnittliche Zahl von 2 - 50 Polyethoxylateinheiten pro Molekül des oberflächenaktiven Stoffs hat.
3. Zusammensetzung nach Anspruch 1 oder 2, in der der oberflächenaktive Stoff ein Blockcopolymer aus Ethylenoxid und Propylenoxid ist.
4. Zusammensetzung nach Anspruch 1 oder 2, in der der oberflächenaktive Stoff ein wasserabweisendes Teil hat, das von einem Alkylphenol, einem Alkohol, oder Ethylendiamin abgeleitet ist.
5. Zusammensetzung nach Anspruch 4, in der der Alkohol ein einwertiger Alkohol ist.
6. Zusammensetzung nach Anspruch 4, in der der Alkohol mehrwertig ist.
7. Zusammensetzung nach Anspruch 6, in der der mehrwertige Alkohol teilweise verestert ist.
8. Zusammensetzung nach einem der Ansprüche 1, 2, 4, 6 oder 7, in der der oberflächenaktive Stoff Polysorbat 20, Polysorbat 40, Polysorbat 60, oder Polysorbat 80 ist.
9. Zusammensetzung nach einem der vorhergehenden Ansprüche, in der das Treibgas von Treibgas 134a, Treibgas 152a und Treibgas 227 ausgewählt wird.
10. Zusammensetzung nach einem der vorhergehenden Ansprüche, in der das Treibgas Treibgas 227 ist.

Patentansprüche für folgende Vertragsstaaten : ES, GR

1. Verfahren zur Herstellung einer Druckaerosolzusammensetzung, das ein Arzneimittel umfasst, ein Fluorkohlen-



wasserstofftreibgas, und einen polyethoxylierten oberflächenaktiven Stoff, und dadurch gekennzeichnet, daß sie kein Lösungsmittel außer dem Treibgas enthält, das die Löslichkeit des oberflächenaktiven Stoffs in dem Treibgas erhöhen kann, wobei das Verfahren umfasst, das Arzneimittel und den oberflächenaktiven Stoff mit dem Treibgas zu mischen.

2. Verfahren nach Anspruch 1, in der der oberflächenaktive Stoff eine durchschnittliche Zahl von 2 - 50 Polyethoxyleinheiten pro Molekül des oberflächenaktiven Stoffs hat.
3. Verfahren nach Anspruch 1 oder 2, in der der oberflächenaktive Stoff ein Blockcopolymer aus Ethylenoxid und Propylenoxid ist.
4. Verfahren nach Anspruch 1 oder 2, in der der oberflächenaktive Stoff ein wasserabweisendes Teil hat, das von einem Alkylphenol, einem Alkohol, oder Ethylendiamin abgeleitet ist.
5. Verfahren nach Anspruch 4, in der der Alkohol ein einwertiger Alkohol ist.
6. Verfahren nach Anspruch 4, in der der Alkohol mehrwertig ist.
7. Verfahren nach Anspruch 6, in der der mehrwertige Alkohol teilweise verestert ist.
8. Verfahren nach einem der Ansprüche 1, 2, 4, 6 oder 7, in der der oberflächenaktive Stoff Polysorbat 20, Polysorbat 40, Polysorbat 60, oder Polysorbat 80 ist.
9. Verfahren nach einem der vorhergehenden Ansprüche, in der das Treibgas von Treibgas 134a, Treibgas 152a und Treibgas 227 ausgewählt wird.
10. Verfahren nach einem der vorhergehenden Ansprüche, in der das Treibgas Treibgas 227 ist.

#### Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, LI, DE, DK, FR, GB, IT, LU, NL, SE

1. Formulation pressurisée en aérosol comportant un médicament, un propulseur hydrofluorocarbure et un tensio-actif polyéthoxylé, caractérisé en ce que la composition ne contient aucun solvant, sauf le propulseur, susceptible d'augmenter la solubilité du tensio-actif dans le propulseur.
2. Formulation selon la revendication 1, dont le tensio-actif comporte un nombre moyen entre 2 à 50 unités de polyéthoxylate par molécule de tensio-actif.
3. Formulation selon la revendication 1 ou 2, dont le tensio-actif est un copolymère bloc d'oxyde d'éthylène et d'oxyde de propylène.
4. Formulation selon la revendication 1 ou 2, dont le tensio-actif comporte une portion hydrophobe dérivée à partir d'un phénol alcoyle, d'un alcool ou de diamine éthylrique.
5. Formulation selon la revendication 4, dont l'alcool est un alcool monohydrique.
6. Formulation selon la revendication 4, dont l'alcool est polyhydrique.
7. Formulation selon la revendication 6, dont l'alcool polyhydrique est partiellement estérifié.
8. Formulation selon l'une ou l'autre des revendications 1, 2, 4, 6 ou 7, dont le tensio-actif est le polysorbate 20, le polysorbate 40, le polysorbate 60 ou le polysorbate 80.
9. Formulation selon l'une ou l'autre des revendications précédentes, dont le propulseur est sélectionné à partir des propulseurs 134a, 152a et 227 respectivement.
10. Formulation selon l'une ou l'autre des revendications précédentes, dont le propulseur est le propulseur 227.

Revendications pour les Etats contractants suivants : ES, GR

- 5 1. Procédé de préparation d'une formulation pressurisée en aérosol comportant un médicament, un propulseur hydrofluorocarboné et un tensio-actif polyéthoxylé, et caractérisé en ce qu'il ne contient aucun solvant sauf le propulseur, susceptible d'augmenter la solubilité du tensio-actif dans le propulseur, ledit procédé comportant le mélange du médicament et du tensio-actif avec le propulseur.
- 10 2. Procédé selon la revendication 1, dont le tensio-actif comporte un nombre moyen entre 2 et 50 unités de polyéthoxylate par molécule de tensio-actif.
- 15 3. Procédé selon la revendication 1, dont le tensio-actif est un copolymère bloc d'oxyde d'éthylène et d'oxyde de propylène.
4. Procédé selon la revendication 1 ou 2, dont le tensio-actif comporte une portion hydrophobe dérivée à partir d'un phénol alcoyle, d'un alcool ou de diamine éthylique.
5. Procédé selon la revendication 4, dont l'alcool est un alcool monohydrique.
- 20 6. Procédé selon la revendication 4, dont l'alcool est polyhydrique.
7. Procédé selon la revendication 6, dont l'alcool polyhydrique est partiellement estérifié.
8. Procédé selon l'une ou l'autre des revendications 1, 2, 4, 6 ou 7, dont le tensio-actif est le polysorbate 20, l'alcool est le polysorbate 40, le polysorbate 60 ou le polysorbate 80.
- 25 9. Procédé selon l'une ou l'autre des revendications précédentes, dont le propulseur est sélectionné à partir des propulseurs 134a, 152a et 227 respectivement.
- 30 10. Procédé selon l'une ou l'autre des revendications précédentes, dont le propulseur est le propulseur 227.